Ankle arthritis predicts polyarticular disease course and unfavourable outcome in children with juvenile idiopathic arthritis

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Abstract

Objective

To evaluate the occurrence, clinical characteristics and prognostic factors associated with ankle arthritis in children with juvenile idiopathic arthritis (JIA).

Methods

440 children with JIA were followed for eight years in a prospective Nordic population-based cohort study. Data on remission was available for 427 of these children. Occurrence of clinically assessed ankle arthritis was analysed in relation to JIA category, clinical characteristics and remission data eight years after disease onset.

Results

In 440 children with JIA, 251 (57%) experienced ankle arthritis during the first eight years of disease. Ankle arthritis was least common in the persistent oligoarticular category (25%) and most common in children with extended oligoarticular (83%) and polyarticular RF-negative (85%) JIA. Children who developed ankle arthritis during the first year of disease were younger at disease onset (median age 4.9 (IQR 2.1–8.8) vs. 6.6 (IQR 2.8–10.1) years, p<0.003) and had more cumulative affected joints at 8-year follow-up (median involved joints 10 (IQR 6-16) vs. 3 (IQR 2-9), p<0.001). The odds ratio for not achieving remission eight years after disease onset, if the ankle joint was involved during the first year of disease was 2.0 (95 % CI:1.3–3.0, p<0.001). Hind-, mid- and forefoot involvements were more common compared to patients without ankle arthritis.

Conclusion

In this Nordic population-based 8-year follow-up study, occurrence of ankle arthritis during the first year was associated with an unfavourable disease outcome. We suggest that ankle arthritis should be recognised in the assessment of prognosis and choice of treatment strategy in JIA.

Key words
ankle, foot, arthritis, juvenile idiopathic arthritis, prognosis

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disorder in childhood and entails a high risk of symptoms continuing into adulthood (1). The ankle joint is described as the second most frequently involved joint, after the knee, and is estimated to be affected in 21-60% of children with JIA (2-10). In recent reports, self-reported foot-related disability has been associated with increased disease activity (11) and the need for improved foot care programmes has been highlighted (11, 12).

The importance of identifying early predictors of disease progression in JIA has been stressed and several studies have mentioned ankle arthritis as such a predictor. Al-Matar *et al*. found an increased likelihood for children with oligoarticular disease to develop extended disease and erosions if ankle and/or wrist joints were involved (2), and Felici *et al*. showed that antinuclear antibody (ANA) positive children with monoarticular ankle arthritis at disease onset were more likely to develop extension to polyarticular disease (13). In a study by Flatø *et al*., ankle and/or toe arthritis within the first six months of disease was predictive of extension to juvenile psoriatic arthritis (14). Furthermore, ankle arthritis has been associated with failure to achieve remission in children with enthesitis-related arthritis (4).

In clinical practice, ankle arthritis has proven to be more resistant to treatment with intra-articular corticosteroid injections (IACI) as compared with knee arthritis, with relapse occurring in 55% of ankle vs. 27% of knee joints (15). The risk of relapse has been estimated to be higher in the ankle and subtalar joints than in other joints, *e.g*. knee and wrist (16, 17). Occurrence of ankle arthritis has also been associated with reduced physical activity in JIA, as assessed using accelerometry (18). Furthermore, the ankle and the elbow joints were found to be more prone to ultrasound-verified subclinical activity in patients in remission (19, 20). In summary, ankle arthritis has previously been associated with increased disease burden, both as a predictor of unfavourable disease and as more difficult to treat in daily clinical practice.

Results from recent studies concerning the epidemiology of ankle arthritis in JIA are, however, problematic to extrapolate to broader populations as these studies are either cross-sectional (3, 4, 9, 21), retrospective (2, 4, 6-8, 21), focused on specific JIA categories (2, 4, 7-10) or conducted before the introduction of today's modern treatment modalities (5, 8, 10). Population-based cohort studies, such as the Nordic JIA cohort study, have the advantage of being representative of the whole disease spectrum and its diverse clinical phenotypes (22, 23).

The aim of this study was to evaluate the occurrence of ankle arthritis in children with JIA in a prospective population-based cohort, to describe clinical characteristics in children with ankle arthritis and to assess associations between ankle arthritis within the first year of disease and remission status eight years after disease onset.

Methods and participants

Participants

The Nordic JIA cohort consists of 500 children, 60 children (12%) were lost to follow-up yielding a cohort of 440 children. These were followed prospectively for a median of 97 months (Inter Quartile Range (IQR) 95–105) in a population-based approach and classified according to the criteria of the International League of Associations for Rheumatology (ILAR). The ILAR category was retrospectively determined for the majority of patients, separately by two of the authors (LB and EN), and based on all available information that was registered at each visit during the study period (24). Disease onset was defined as the date when the child, according to anamnestic information fulfilled the criteria for active arthritis or experienced the onset of systemic features, not necessarily confirmed by a physician. The first examination as part of this Nordic cohort was at six months of disease duration with an acceptance of -1 to +2 months deviation from the exact date, resulting in a median time of 7 months (IQR of 6–8 months). A study visit was planned every 6 months during the first year after disease onset and then every 1–2 years during the observation period.

In some centres, however, fewer visits were registered, and totally a mean of five visits were registered per participant. Children with only one visit were excluded from the study. At each visit clinical data the number of currently active joint together with joints that had been active since last visit were recorded. The number of cumulative (ever active) involved joints from both upper and lower extremities was based on the data reported into the Nordic database and collected after eight years of disease duration. Further details of the study design and disease characteristics of the participants have been extensively described elsewhere (23).

Outcome measures

The following demographics and disease characteristics within the first six months of disease were obtained from the Nordic JIA cohort database from the first visit: Age at disease onset, human leukocyte antigen B27 (HLA-B27) and rheumatoid factor (RF) assessed using ELISA (Denmark), nephelometry (Norway and Sweden), latex agglutination testing (Sweden), and immunoturbidimetric testing (Finland), antinuclear antibody (ANA), performed twice, at least three months apart. ANAs included in analyses were measured using immunofluorescence on HEp-2 cells and were interpreted as positive or negative according to the reference values used by the local laboratory in each country. Also, the maximum values of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) assessed during the first six months after diagnosis were collected. C-reactive protein was measured in immunoassays, with upper normal values ranging from <3 to <10 mg/litre; in the study protocol, the cut-off value for the whole population was set to <10 mg/litre.

The following variables were obtained from the Nordic cohort database at the 8-year follow-up: ILAR category and remission status according to the preliminary criteria of Wallace *et al*. (25). The cumulative number of affected joints during the first eight years of disease in the lower extremities was summarised for ankle (talocrural joint), subtalar, tarsal, metatarsophalangeal (MTP) 1–5, interphalangeal distal and proximal (toe) 1–5, knee and hip joints. The first occurrence of arthritis in specific joints was derived from the Nordic database within the present study. Thus, a specific joint was only counted at first presentation even if it presented at several occasions during the disease course. Arthritis was manually assessed by experienced paediatric rheumatologists and was defined using the ILAR criteria. Thus, arthritis was defined as swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness, which persists for at least 6 weeks, is observed by a physician, and is not due to primarily mechanical disorders or to other identifiable causes (24). Uveitis was defined as within the ILAR criteria as chronic uveitis diagnosed by an ophthalmologist (24). Self-reported physical function at the 8-year follow-up was assessed using the Child Health Assessment Questionnaire (CHAQ) (score 0–3, 3 = severe disability) for patients younger than 18 years and the Health Assessment Questionnaire (HAQ) (score 0–3, 3 = severe disability) for patients older than 18 years (26-31). Scores for the CHAQ were provided by children who were older than nine years of age and by the parents of younger children. From the CHAQ, the subscales of walking, rising and activity were incorporated into a score representing lower extremity activities (CHAQlow/ HAQlow). The sum of the scores from these three subscales was divided by three, yielding a score from 0 to 3 (3 = severe disability).

Ethics

The Research Ethical Committees in each respective country gave their approval according to national practice and legislation. Written informed consent was obtained from children ≥16 years of age and from parents/legal guardians of children aged <16 years.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences, version 22 (SPSS Inc., Chicago, IL, USA). Demographics and disease characteristics were described using median and interquartile range (IQR), or total number and percent of study cohort. Statistical analysis of differences between children with and without ankle arthritis during the first year of disease was estimated using χ^2 test (Fisher's exact test 2-sided) for comparison of dichotomous variables and the Mann-Whitney U-test for comparison of non-parametric data.

Multiple logistic regression analyses were performed in order to identify the association between ankle arthritis within the first year and failure of remission eight years after disease onset. The dichotomised variable remission (remission without medication) versus not being in remission (remission with medication or not in remission) was used as dependent variable in the regression model. The following independent variables were included: presence of ankle, knee and hip arthritis during the first year of disease, presence of HLA-B27, gender, and age at disease onset. Measures obtained during the first year were considered for inclusion, thus, CHAQ and presence of uveitis were not considered. Highest value of ESR, CRP and presence of ANA were excluded due to reduced sample size, 47% of the participants were excluded from regression analysis if these three variables were included. However, running a multiple regression analysis and including these three variables did not change the results. A forward step-wise inclusion of variables was performed and the independent variables associated with the dependent variable ($p<0.05$ in the univariate analysis) were included in the multiple regression analysis. Results of the regression models are shown as the odds ratio (OR) and 95% confidence interval (95 % CI). The level of significance was set at 5% ($p<0.05$).

Results

Participants and clinical characteristics

The cohort of patients included 440 children, 66% girls, with a median age of 5.5 (IQR 2.5–9.7) years at disease onset. Data on remission status was available for 427 of the children at 8-year follow-up and these data were considered in the regression analyses.

Table I. Frequency of clinically assessed arthritis in joints of lower limbs, at the 8-year follow-up visit for patients in the Nordic JIA cohort, and its distribution for each ILAR category.

Characteristics	JIA category									
	Total cohort n=440 n (%)	Disease duration (months) at first registration of arthritis median (IQR)	Systemic n=18 n (%)	Oligoarticular persistent n=132 n (%)	Oligoarticular extended n=78 n (%)	Polyarticular RF negative n=80 n (%)	Polyarticular RF positive n=3 n (%)	Psoriatic n=14 n (%)	Enthesitis-related n=49 n (%)	Undifferentiated n= 66 n (%)
Gender female	291 (66)	–	12 (67)	86 (65)	60 (77)	61 (76)	2 (67)	7 (59)	16 (33)	47 (71)
Ankle	251 (57)	7 (6-13)	11 (61)	34 (25)	65 (83)	68 (85)	1 (33)	6 (43)	27 (55)	39 (59)
Subtalar	94 (21)	7 (6-91)	3 (17)	7 (5)	25 (32)	30 (38)	0 (0)	0 (0)	14 (29)	15 (23)
Tarsal	75 (17)	12 (6-97)	1 (6)	5 (4)	26 (33)	28 (35)	0(0)	0 (0)	9 (18)	6 (9)
MTP and/or toe	130 (30)	8 (6-31)	2 (11)	16 (12)	28 (36)	39 (49)	1 (33)	2 (14)	20 (41)	22 (33)
Knee	357 (81)	7 (6-12)	15 (83)	99 (75)	73 (94)	67 (84)	3 (100)	11 (79)	36 (74)	53 (80)
Hip	110 (25)	12 (6-36)	8 (44)	17 (13)	19 (24)	23 (29)	0 (0)	6 (43)	18 (37)	19 (29)
Cumulative n. of joints with clinically assessed arthritis*	6 (2-12)	–	6 (3-13)	2 (1-3)	9 (6-12)	13 (8-23)	13	7 (3-9)	5 (3-13)	10 (4-17)

Values represent number (percent), if not otherwise indicated, of total patients in each category with the arthritis registered within eight years of disease. The first examination as part of this Nordic cohort was at six months of disease duration with an acceptance of -1 to +2 months deviation from the exact date. Only first occurrence of arthritis in specific joints during the first eight years of disease was registered. Disease duration at the first registration of clinically assessed arthritis in specific joints is presented in column II. *Total number of all ever affected joints during the study period including both lower and upper extremities. MTP; Metatarsophalangeal joints; nb; number; IQR; interquartile range.

Occurrence of ankle arthritis

In total, 251 (57%) of the 440 children experienced ankle arthritis during the first eight years of disease (Table I). The ankle was the second most frequently involved joint, after the knee (81%), and was involved early in the disease course, at a median of 7 months (IQR 6–13) after disease onset. Ankle arthritis was least common in the persistent oligoarticular category (25%) and most common in children with the extended oligoarticular (83%) and polyarticular RF-negative disease (85 %) (Table I). Of the 251 children with JIA presenting with ankle arthritis, the arthritis started in 73% the first year and in 84% within the first two years of disease.

Clinical characteristics in children with ankle arthritis

Children with a history of ankle arthritis during the first year of disease differed from those without ankle arthritis during the first year of disease in several aspects (Table II). They were younger at disease onset, had higher levels of ESR and CRP during the first six months of disease and a higher number of cumulative affected joints eight years after disease onset compared with children without ankle arthritis within the first year of disease. There was no difference between children with and without a history of ankle arthritis regarding presence of ANA, HLA-B27 or uveitis. At the 8-year follow-up visit, ankle arthritis within the first year if disease were: associated with failure to achieve remission and to a higher CHAQ/HAQ scores, indicating increased physical disability. However, ankle arthritis was not associated with a worse score in $CHAQ_{low}/HAQ_{low}$, which represents disability related to lower extremity activities.

Subtalar, tarsal, MTP and toe involvements were significantly more common in children with ankle arthritis as compared with those without. In the 94 children with subtalar arthritis at some time point during the first eight years of disease, 83 (88%) had additional ankle arthritis, and for the 75 children with tarsal involvement, 81% had ankle arthritis.

Associations between ankle arthritis and failure to achieve remission

A total of 399 children were included in a multiple regression analysis and adjustments were made for: knee and hip arthritis during the first year, age at disease onset, presence of HLA-B27 and gender. In this regression analysis, occurrence of arthritis within the first year of disease was associated with failure to achieve remission at eight year after disease onset, OR 2.0 (95% CI 1.3–3.0) (Table III).

Discussion

In this study data from 440 children with JIA followed for eight years of disease were used to study the predictive value of early ankle arthritis. Ankle arthritis was common, occurred early in the disease, and was associated with a polyarticular disease course and failure to achieve remission.

The strength of this study is the prospective, longitudinal and population-based approach, which supports the validity of the results. The cohort is multinational with several experienced physicians assessing the children. All ILAR categories were represented, even if the number of patients in some categories was small, which restricts subgroup analysis. An important limitation of the study was that ankle arthritis was clinically evaluated without verification with ultrasound or other imaging modalities, which might lead to an underestimation of the number of affected joints, as ultrasound has proven superior in detecting synovitis (32-34). Also, performing ultrasound of the ankle might have added further information such as distinction between talocrural, subtalar and tarsal involvement and detection of subclinical inflammation.

In accordance with previous publications, ankle arthritis occurred in approximately 60% of the cohort during the first eight years of disease (7, 8,

Table II. Clinical characteristics for children with and without occurrence of ankle arthritis during first year of disease.

Characteristics	Total group n		Ankle arthritis first year of disease n		No ankle arthritis first year of disease n		*p*-value Ankle *vs.* no ankle
Age at disease onset, median years (IQR)	440	5.5 (2.5-9.7)	186	4.9 (2.1-8.8)	254	6.6 (2.8-10.1)	0.003[b]
Gender, female n (% of total)	440	291 (66)	186	127 (68)	254	164 (65)	0.475[a]
ANA positive, n (% of total)	391	107 (27)	160	46 (29)	231	61 (26)	0.645[a]
HLA-B27 positive, n (% of total)	410	86 (21)	173	33 (19)	237	53 (22)	0.462[a]
Assessments, first six month of disease							
ESR mm/hour, median (IQR)	333	35 (16-55)	150	45 (26-77)	183	24 (12-48)	<0.001[b]
CRP mg/litre, median (IQR)	332	14 (0-35)	143	28 (10-56)	189	10 (0-23)	<0.001[b]
Assessments, first eight years of disease							
Cumulative joints, median (IQR)*	440	6 (2-12)	186	10 (6-16)	254	3 (2-9)	<0.001[b]
Not in remission at eight years follow-up, n (%)	427	246 (42)	183	120 (66)	244	126 (52)	0.004[a]
Uveitis, n (% of total)	425	89 (21)	179	36 (20)	246	53 (22)	0.809[a]
$CHAQ_{low}/HAQ_{low}$, n (%) >0	358	35 (10)	149	18 (12)	209	17 (8)	0.279[a]
CHAQ/HAQ, n (%) >0	359	110 (31)	149	56 (38)	210	54 (26)	0.020[a]

[a]Fisher's exact test 2-sided, [b]Mann-Whitney U-test. n: number, ANA: Antinuclear antibody, HLA-B27: Human Leukocyte Antigen B27, (C)HAQ: (Child) Health Assessment Questionnaire. Values for the C-reactive protein (CRP) level and the erythrocyte sedimentation rate (ESR) are the maximum values reported during the first 6 months after disease onset". We have added "CHAQlow; Child Health Assessment Questionnaire lower extremity; percent of children rating > 0, indicating physical disability related to the lower extremities at the eight year follow-up. *Cumulative number of arthritis in specific joints that have been active during the first eight years of disease.

Table III. Odds ratios for failure to achieve remission eight years after disease onset, if the ankle joint had been affected during the first year of disease, in children with JIA from the Nordic cohort.

Joint involvements first year	Total number n=399	Not in remission n=237	Univariate analysis OR (95% CI)	*p*-value	Multivariate analysis OR (95% CI)	*p*-value
Ankle, n (% of total)	172	117 (68)	1.9 (1.3-2.9)	**0.002**	2.0 (1.3-3.0)	**0.001**
Knee, n (% of total)	251	147 (59)	0.9 (0.6-1.4)	0.659		
Hip, n (% of total)	52	31 (60)	1.1 (0.6-1.8)	0.973		

OR: Odds ratio; CI: Confidence Intervals; n: number; HLA-B27: Human Leukocyte Antigen B27; Univariate analysis: no adjustments. Multivariate analysis; ankle arthritis with adjustments for occurrence of knee and hip arthritis during the first year. gender, age at disease onset and occurrence of HLAB-27.

10). It was least common in children with persistent oligoarticular disease and most common in those with extended oligoarticular and polyarticular disease. While the occurrence of ankle arthritis in children with JIA was comparable between studies, the proportion presenting with ankle arthritis at onset has shown more diversity, with numbers varying from 21% to 58% in different studies (2, 6, 8, 21). This variation can be due to differences in study designs, for example the use of retrospective analysis, and inclusion of children from different ILAR categories. In our study, ankle arthritis together with knee arthritis occurred early in the disease course, at a median time of seven months after disease onset. This is in accordance with Hemke *et al*. They showed a steep increase in occurrence of ankle arthritis in the first six months of disease and the cumulative number plateaued after the first year (6).

In our study, the ankle seems to represent involvement of the whole foot. Our results show that it was uncommon to have subtalar arthritis without ankle arthritis. Furthermore, tarsal joints, MTP joints and toes were more frequently involved in children with ankle arthritis than in those without.

Clinical characteristics of children with ankle arthritis during the first year of disease in our study included: younger age at disease onset, polyarticular disease course, elevated ESR and CRP levels at disease onset, and increased risk of failure to achieve remission after eight years of disease. Ankle arthritis has previously been associated with polyarticular disease and extension to a polyarticular disease course in children with an oligoarticular onset (2, 13, 14). Thus, children with oligoarticular onset presenting with ankle arthritis are at a higher risk of disease progression. Our results are comparable to others, although we have found no other study that has included all ILAR categories. Al-Matar *et al*. studied the oligoarticular category and demonstrated that ankle and/or wrist involvement together with symmetric disease and elevated ESR levels during the first six months of disease predicted extension to polyarticular disease course (2). Furthermore, Felici *et al*. studied the disease course in a well-defined group of 195 ANA positive children with oligoarticular persistent and polyarticular disease, and concluded that children presenting with ankle monoarthritis at disease onset were more likely to develop extension to polyarticular disease as compared with those presenting with

symptoms in other joints (13). Much like in our study, Felici *et al*. defined ANA positivity using immunofluorescence on HEp-2 cells, as this method has showed superior clinical validity (35), but neither we nor others have found an association between positive ANA and ankle arthritis (7). Ankle arthritis during the first year of disease was not associated with presence of HLA-B27. HLA-B27 has already been associated with failure to achieve remission in this Nordic JIA cohort (36) and our present study adds occurrence of ankle arthritis during the first year of disease as another predictor.

In our study, knee arthritis also presented early in the disease course. However, its predictive value of unfavourable outcome was low, since knee arthritis occurred in 80% of the total cohort and was distributed evenly between the ILAR categories, including in 75% of the oligoarticular persistent category.

We aimed to study the presence and impact of ankle arthritis on disease progression in relation to other joints in the lower extremities, but not to include all joints of the body in the analyses. Thus, the upper extremity joints are not individually represented, but are indirectly acknowledged in the total number of cumulative joints and in the CHAQ score, which tends to focus on upper extremity activities. Children who experienced ankle arthritis had a higher CHAQ score after eight years of disease as compared with those without ankle arthritis. The $CHAQ_{low}$ score, including three sub-scales dealing with lower extremity activities, did not differ significantly between the groups. Thus, ankle arthritis seems to be a marker of extension to polyarticular disease just as the wrist has often been mentioned together with the ankle in epidemiologic studies predicting progression of disease.

There are two clinical implications following the results from this study: first, the increased awareness of risk of extension to polyarticular disease course in children presenting with ankle arthritis and oligoarticular pattern and second, the high frequency of ankle arthritis. These implications must be seen in the light of existing literature pointing at diagnostic and treatment challenges, such as resistance to treatment with IACI (15), increased risk of relapse (16, 17), and subclinical activity (19, 20). Our study suggests that occurrence of ankle arthritis denotes a polyarticular disease course with onset at young age, an increased risk of not achieving remission, which probably warrants more aggressive medical therapy. It is however important to acknowledge that ankle arthritis occurred to a higher extent in ILAR categories already known to have a worse prognosis, such as the polyarticular and oligoarticular extended category. Thus, it could be argued that ankle arthritis is a marker of these categories/groups rather than a predictor of worse prognosis. Improvements in clinical practice for children presenting with ankle arthritis could include image-guided assessment, in order to detect arthritis extension early, as well as shorter follow-up intervals.

Conclusions

Ankle arthritis is common in JIA, is associated with a polyarticular disease course in young children and with failure to achieve remission. We suggest that ankle arthritis should be recognised in the assessment of prognosis and choice of treatment strategy in JIA.

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